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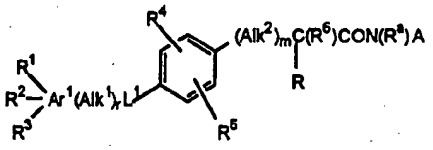

(1)

(57) Abstract

Phenylalkanoic acid derivatives of formula (1) are described; wherein Ar^1 is an aromatic or heteroaromatic group; L^1 is a covalent bond or a linker atom or group; A is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group; R is a carboxylic acid ($-CO^2H$) or a derivative thereof; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of alpha 4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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PHENYLALKANOIC ACID DERIVATIVES AS INHIBITORS OF ALPHA4 INTEGRINS

This invention relates to a series of phenylalkanoic acid derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A. *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like α4β1, binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between α4β7 and MAdCAM-1 may also be important at

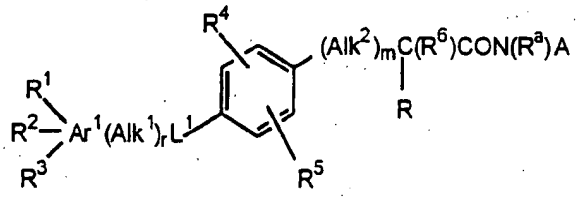
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

Ar^1 is an aromatic or heteroaromatic group;

R^1, R^2, R^3, R^4 and R^5 which may be the same or different is each an atom or group $-L^2(Alk^3)_tL^3(R^7)_u$ in which L^2 and L^3 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^3 is an aliphatic or heteroaliphatic chain and R^7 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-SR^8$, $-NR^8R^9$ [where R^9 is as just defined for R^8 and may be the same or different], $-NO_2$, -CN, $-CO_2R^8$, $-SO_3H$, $-S(O)R^8$, $-SO_2R^8$, $-OCO_2R^8$, $-CONR^8R^9$, $-OCONR^8R^9$, $-CSNR^8R^9$, $-COR^8$, $-OCOR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^9)(R^{10})$, [where R^{10} is a hydrogen atom or an optionally substituted alkyl group] $-N(R^8)CSN(R^9)(R^{10})$ or $-N(R^8)SO_2N(R^9)(R^{10})$;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a covalent bond or a linker atom or group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^6 is a hydrogen atom or a methyl group;

r is zero or the integer 1;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

R^a is a hydrogen atom or a methyl group;

A is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and

mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include $-CO_2Alk^5$ and $-CONR^8R^9$ groups as described herein.

In general, the substituents R^1, R^2 and R^3 in compounds of the invention may be positioned on any available carbon atom, or, when present, nitrogen atom in the aromatic or heteroaromatic group represented by Ar^1.

When Alk^1 and/or the group A is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.

Heteroaliphatic chains represented by Alk^1 and/or the group A include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^4 where L^4 is as defined above for L^1 when L^1 is a linker atom or group. Each L^4 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.

Particular examples of aliphatic chains represented by Alk^1 and/or the group A include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$, or $-(CH_2)_2CC-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^4 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-L^4CH_2-$, $-CH_2L^4CH_2-$, $-L^4(CH_2)_2-$, $-CH_2L^4(CH_2)_2-$, $-(CH_2)_2L^4CH_2-$, $-L^4(CH_2)_3-$ and $-(CH_2)_2L^4(CH_2)_2-$ chains. The optional

substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^{12}$ and $-N(R^{12})_2$ groups where R^{12} is an optionally substituted straight or branched alkyl group as defined below for R^{11}. Where two R^{12} groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$ $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3}alkylene chain. Particular examples include $-CH_2-$, $-CH(CH_3)-$ and $-(CH_2)_2-$.

When in the compounds of formula (1) L^1, L^2 and/or L^3 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{11})-$ [where R^{11} is a hydrogen atom or an optionally substituted alkyl group], $-CON(R^{11})-$, $-OC(O)N(R^{11})-$, $-CSN(R^{11})-$, $-N(R^{11})CO-$, $-N(R^{11})C(O)O-$, $-N(R^{11})CS-$, $-S(O)_2N(R^{11})-$, $-N(R^{11})S(O)_2-$, $-N(R^{11})CON(R^{11})-$, $-N(R^{11})CSN(R^{11})-$, or $-N(R^{11})SO_2N(R^{11})-$ groups. Where the linker group contains two R^{11} substituents, these may be the same or different.

When R^7, R^8, R^9, R^{10} and/or R^{11} in the compounds of formula (1) is an alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy e.g. methoxy or ethoxy groups.

When Alk^3 is present in the compounds of formula (1) as an aliphatic or heteroaliphatic chain it may be for example any of the above-mentioned C_{1-10}aliphatic or heteroaliphatic chains described for Alk^1.

Halogen atoms represented by R^7 in compounds of the invention include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by R^1, R^2, R^3, R^4 and R^5 in compounds of formula (1) include atoms or groups $-L^2Alk^3L^3R^7$, $-L^2Alk^3R^7$, $-L^2R^7$ and $-Alk^3R^7$ wherein L^2, Alk^3, L^3 and R^7 are as defined above. Particular examples of such substituents include $-L^2CH_2L^3R^7$, $-L^2CH(CH_3)L^3R^7$, $-L^2CH(CH_2)_2L^3R^7$, $-L^2CH_2R^7$, $-L^2CH(CH_3)R^7$, $-L^2(CH_2)_2R^7$, $-CH_2R^7$, $-CH(CH_3)R^7$, $(CH_2)_2R^7$ and $-R^7$ groups.

Thus each of R^1, R^2, R^3, R^4 and R^5 in compounds of the invention may be for example a hydrogen atom, a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^5$ [where Alk^5 is as defined below], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphinyl e.g. methylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylamino-

sulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethyl-aminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino group.

Optionally substituted cycloaliphatic groups represented by the group A in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenylgroups.

Optionally substituted heterocycloaliphatic groups represented by the group A include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl,

e.g. C_{3-7} heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7} hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^4 as defined above.

Optionally substituted polycycloaliphatic groups represented by the group A include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by the group A include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^4 atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups represented by the group A include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the R^1 and R^6 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups represented by the group A include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk)_vR^{12}$ groups in which Alk is a straight or branched C_{1-3}alkylene chain, v is zero or an integer 1 and R^{12} is

a -OH, -SH, $-N(R^{11a})_2$, -CN, $-CO_2R^{11a}$, $-NO_2$, $-CON(R^{11a})_2$, $-CSN(R^{11a})_2$, $-COR^{11a}$, $-CSN(R^{11a})_2$, $-N(R^{11a})COR^{11a}$, $-N(R^{11a})CSR^{11a}$, $-SO_2N(R^{11a})_2$, $-N(R^{11a})SO_2R^{11a}$, $-N(R^{11a})CON(R^{11a})_2$, $-N(R^{11a})CSN(R^{11a})$ or $-N(R^{11a})SO_2N(R^{11a})_2$ group in which R^{11a} is an atom or group as defined herein for R^{11}. Additionally, when the group A is a heterocyclo-aliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^6)_qR^{15}$ in which L^5 is -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^{11})-$, $-CSN(R^{11})-$, $-SON(R^{11})-$ or $SO_2N(R^{11})-$; p is zero or an integer 1; Alk^6 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{15} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^6 include those optionally substituted chains described above for Alk^1.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocyclo-aliphatic groups represented by R^{15} include those groups just described for the group A. Optional substituents which may be present on these groups include those described above in relation to Alk^1 aliphatic and heteroaliphatic chains.

Aromatic groups represented by the group Ar^1 and/or A in compounds of the invention include for example monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups. Aromatic groups represented by the group A may be optionally substituted by one, two, three or more R^{13} atoms or groups as defined below.

Heteroaromatic groups represented by the group Ar^1 and/or A in the compounds of formula (1) include for example C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or

six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, qunoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group A include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^4(R^{13a})_m$, where R^{13a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^3(R^{13a})_m$, aryl or heteroaryl group], $-CSR^{14}$, $-SO_3H$, $-SO_2R^{14}$ $-SO_2NH_2$, $-SO_2NHR^{14}$ $SO_2N(R^{14})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON[R^{14}]_2$, $-CSN(R^{14})_2$, $-N(R^{11})SO_2R^{14}$, $-N(SO_2R^{14})_2$, $-NH(R^{11})SO_2NH_2$, $-N(R^{11})SO_2NHR^{14}$, $-N(R^{11})SO_2N(R^{14})_2$, $-N(R^{11})COR^{14}$, $-N(R^{11})CONH_2$, $-N(R^{11})CONHR^{14}$, $-N(R^{11})CON(R^{14})_2$, $-N(R^{11})CSNH_2$, $-N(R^{11})CSNHR^{14}$, $-N(R^{11})CSN(R^{14})_2$, $-N(R^{11})CSR^{14}$, $-N(R^{11})C(O)OR^{14}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{11})-$, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{11})SO_2NHet^1$, $-N(R^{11})CONHet^1$,

$-N(R^{11})CSNHet^1$, $-SO_2N(R^{11})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{11})-$, -C(O)- or -C(S)- groups], $-Het^2$, $-CON(R^{11})Het^2$, $-CSN(R^{11})Het^2$, $-N(R^{11})CON(R^{11})Het^2$, $-N(R^{11})CSN(R^{11})Het^2$, aryl or heteroaryl group; Alk^4 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{15})-$ groups [where R^{15} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.

When in the group $-Alk^4(R^{13a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in $-Alk^4$. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^4$. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group $-NHR^{14}$ [where R^{14} is as defined above] or a group $-N(R^{14})_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^5$ wherein Alk^5 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally

substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{13a} substituents described above.

When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{12})-$ groups.

Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Ar^2. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{13} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ or $-Het^2$ include those R^7 substituents described above.

Particularly useful atoms or groups represented by R^{13} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperadinyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl,

e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy, ethoxy or propoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, optionally substituted C_{6-12}arylC_{1-6}alkylamino e.g. benzylamino, amino ($-NH_2$), aminoC_{1-6}alkylamino e.g. aminomethylamino, aminoethylamino or aminopropylamino, aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino, e.g. hydroxymethylamino or hydroxyethylamino, Het^1NC_{1-6}alkylamino e.g. morpholinopropylamino or piperidinylethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^5$ [where Alk^5 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl, thioethyl or thiopropyl, thioC_{1-6}alkylC_{6-12}aryl e.g. thiobenzyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), C-$_{1-6}$alkylsulphinyl e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonyl-

methylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6} alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6} alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by Ar^2.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived

from inorganic or organic acids, and salts derived from inorganic and organic bases.

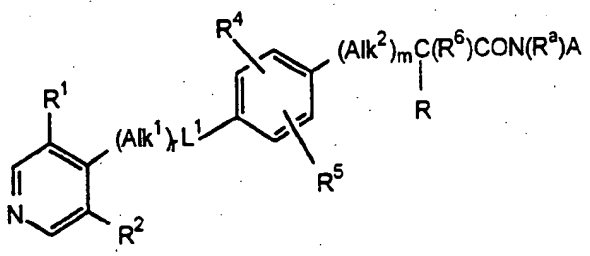
Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In the compounds according to the invention the group Ar^1 is preferably a phenyl or monocyclic heteroaromatic group. Particularly useful groups of this type are five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. R^1, R^2 and R^3 attached to these Ar^1 groups may each be a hydrogen atom or one of the other atoms or groups generally and particularly described above in relation to R^1, R^2 and R^3. Particularly useful atoms or groups include halogen atoms or alkyl, $-OR^8$, $-SR^8$, NR^8R^9, $-NO_2$ or -CN groups as described above in relation to the compounds of formula (1).

A particularly useful group of compounds according to the invention has the formula (2):



(2)

wherein R^1 and R^2, which may be the same or different is each an atom or group $-L^2(Alk^3)_tL^3(R^7)_u$ in which L^2, Alk^3, t, L^3, R^7 and u are as defined for formula (1) provided that R^1 and R^2 are not both hydrogen atoms; Alk^1, Alk^2, m, r, L^1, R^4, R^5, R^6, R^a, A and R are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

R^1 and R^2 in compounds of formula (2) and in general in compounds of formula (1) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R^1 and R^2 substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially $-CF_3$, $-CHF_2$ or $-CH_2F$, methoxy or halomethoxy, especially $-OCF_3$, $-OCHF_2$ or $-OCH_2F$ groups.

R^3 in compounds of the invention is in particular a hydrogen atom.

R in the compounds of formulae (1) and (2) is preferably a $-CO_2H$ group.

When present, the aliphatic chain represented by Alk^1 in compounds of formulae (1) and (2) is preferably a $-CH_2-$ chain.

In general in compounds of formulae (1) and (2) $-(Alk^1)_rL^1-$ is preferably $-CH_2O-$ or $-CON(R^{11})-$.

In compounds of formulae (1) and (2) m is preferably 1 and Alk^2 is preferably $-CH_2-$.

R^4 and R^5 in the compounds of formulae (1) and (2) may be the same or different and is each preferably a hydrogen or halogen atom or an alkyl, alkoxy, hydroxy, nitro, cyano or $-NR^8R^9$ group.

R^6 and R^a in the compounds of formulae (1) and (2) is each preferably a hydrogen atom.

In general in compounds of formulae (1) and (2) the group A may especially be an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted pyridyl groups. Optional substituents on these groups include in particular R^{13} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^5)_p(Alk^6)_qR^{15}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group.

Especially useful A groups include optionally sustituted phenyl or pyridyl groups.

Particularly useful R^{13} substituents in compounds of the invention include a halogen atom, especially fluorine or chlorine, optionally substituted morpholinyl, optionally substituted thiomorpholinyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, thioC_{1-6}alkyl, especially thiomethyl, thioethyl or thiopropyl, optionally substituted thiobenzyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkyloxy, especially methoxy, ethoxy or propoxy, optionally substituted benzyloxy, haloC_{1-6}alkoxy, especially trifluoromethoxy and difluoromethoxy, C_{1-6}alkylamino, especially propylamino, C_{1-6}dialkylamino, especially dimethylamino or diethylamino, optionally substituted C_{6-12}arylC_{1-6}alkylamino, aminoC_{1-6}alkylamino, especially 3-aminopropylamino, Het^1NC_{1-6}alkylamino, especially 3-morpholiopropyl-amino, optionally substituted phenoxy, hydroxyC_{1-6}alkylamino, nitro, carboxyl, $-CO_2Alk^5$ [where R^5 is as defined above], especially carboxymethyl and carbonyethyl, carboxamido, C_{1-6}alkylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, C_{1-6}alkanoyl, optionally substituted benzoyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylaminosulphonyoyl, C_{1-}

$_{6}$dialkylaminosulphonyl, C_{1-6}alkylamino-carbonyl and C_{1-6}dialkylaminocarbonyl.

Particularly useful $-(L^5)_p(Alk^6)_qR^{15}$ groups include those in which L^5 is a -CO- group. Alk^6 in these groups is preferably present (i.e. q is preferably an integer 1) and in particular is a $-CH_2-$chain. Compounds of this type in which R^{15} is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred. Particularly useful optional substituents on these groups include those R^{13} groups just mentioned.

Particularly useful compounds according to the invention include:
3-(2,6-Dichloroanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoic acid;
3-(2,6-Dimethoxyanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino] benzyl}-3-oxopropanoic acid;
2-{4-[3,5-Dichloroisonicotinoyl)amino]benzyl}-3-[(3,5-dichloro-4-pyridinyl)amino]-3-oxapropanoic acid;
2-{4-[(2,6-Dichlorobenzoyl)amino]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid;
2-{4-[(2,6-Dichlorobenzyl)oxy]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

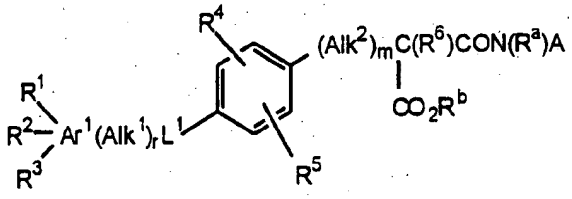
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for

parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1-R^6, Ar^1, L^1, Alk^1, Alk^2, m, r, A, R^a and R when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (3):

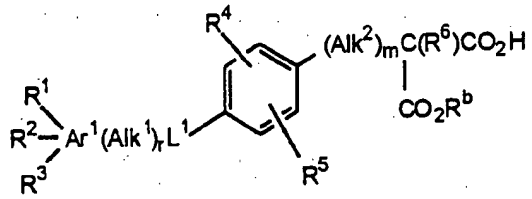


(3)

where R^b is an alkyl group, for example a C_{1-6}alkyl group as described above.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^b, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium or potassium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (3) may be prepared by coupling an acid of formula (4):



(4)

or an active derivative thereof with an amine $ANHR^a$. Active derivatives of acids of formula (4) include anhydrides, esters and halides and may be obtained by standard procedures and may be obtained by standard procedures, for example as described in the Examples hereinafter.

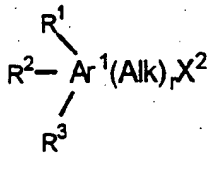
The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out with an active derivative of the acid of formula (4) in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or N,N-diisopropylethylamine, or a cyclic amine, such as N-methylmorpholine, or a hydride, such as sodium hydride in an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature.

Where an acid of formula (4) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclo-

hexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxy-benzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine $ANHR^a$.

The acids of formula (4) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions as described below and in the Examples hereinafter. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds. Additionally, although a number of the intermediate amines $ANHR^a$ for use in the coupling reaction described above are known, others can be derived therefrom using these standard synthetic methods.

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$, $-L^2H$, or $-L^3H$ group (where L^1, L^2 and L^3 is each a linker atom or group) may be treated with an alkylating agent:



, $(R^7)_uL^3Alk^3_tX^2$ or $R^{7a}X^2$ respectively in which X^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group, and R^{7a} is an alkyl group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as

dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$, $-L^2H$ or $-L^3H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^2 is replaced by a $-C(O)X^3$, $C(S)X^3$, $-N(R^8)COX^3$ or $-N(R^8)C(S)X^3$ group in which X^3 is a leaving atom or group as described for X^2. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation or thioacylation may be carried out under the same conditions with an acid or thioacid (for example one of the alkylating agents described above in which X^2 is replaced by a $-CO_2H$ or -COSH group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^2 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$, $-L^2H$ or $-L^3H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^2 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^8$ or $-CO_2Alk^5$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^8 or Alk^5. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^8$ or $-OR^{14}$ groups [where R^8 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{14}$ group (where R^{14} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2Alk^5$ or CO_2R^8] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^8$ group by coupling with a reagent R^8OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1, L^2 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suit able solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystalliation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - N-methylmorpholine; EtOAc - ethyl acetate;

MeOH - methanol;
DCM - dichloromethane;
DMF - dimethylformamide;
Me - methyl;
THF - tetrahydrofuran;
DMSO - dimethylsulphoxide;
All NMR's were obtained at 300MHz.

BOC - butoxycarbonyl;
AcOH - acetic acid;
Ar - aryl;
Et_2O - diethyl ether;
EtOH - ethanol;

INTERMEDIATE 1

{4-[(2,6-Dichlorobenzyl)oxy]phenyl}methanol

A solution of 4-(hydroxymethyl)phenol (38.0g, 0.31mmol) and 2,6-dichlorobenzyl bromide (73.4g, 0.31mmol) in DMF (500ml) was treated with caesium carbonate (100g, 0.31mmol) and heated to 60° for 16h. The mixture was cooled to room temperature and the solvent evaporated in vacuo. The residue was partitioned between EtOAc (250ml) and water (250ml), the aqueous layer was separated and extracted with EtOAc (250ml) and the combined organic layers washed with 10% hydrochloric acid (100ml), $NaHCO_3$ solution (100ml) and brine (200ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound as a brown oil (88.4g) which was used without further purification. δH ($CDCl_3$) 7.38-7.21 (5H, m, ArH), 7.02 (2H, d, J 8.7Hz, ArH), 5.28 (2H, s, CH_2OAr) and 4.63 (2H, s, CH_2OH).

INTERMEDIATE 2

4-(Bromomethyl)phenyl(2,6-dichlorobenzyl)ether

Thionyl bromide (78g, 0.38mmol) was added dropwise to an ice cold solution of Intermediate 1 (88.4g, 0.31mmol), in toluene (500ml). On completion of addition the reaction was warmed to room temperature and stirred for 2h, then washed with water (200ml). The aqueous washings were extracted with Et_2O (2 x 200ml) and the combined organic layers washed with water (200ml), and $NaHCO_3$ solution (3 x 200ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give a brown oil that was recrystallised from hexane to give the title compound (73.8g, 69%) as white crystals. δH ($CDCl_3$) 7.36 (4H, m, Ar-H), 7.25 (1H, m, Ar-H), 6.98 (2H, d, J 8.7Hz), 5.27 (2H, s, CH_2OAr) and 4.51 (2H, s, CH_2Br).

INTERMEDIATE 3

Dimethyl 2-{4-[(2,6-dichlorobenzyl)oxy]benzyl}malonate

Sodium metal (1.83g, 80mmol) was added to MeOH (100ml) and stirred until dissolved. Dimethyl malonate (9.55g, 72.5mmol) was added to this solution dropwise and the reaction stirred for 20 mins. A solution of the compound of Intermediate 2 (25.0g, 72.5mmol) in THF (200ml) was added by cannula over a period of 1.5h. The reaction was stirred for 1h on completion of the addition and quenched with water (100ml). The mixture was concentrated in vacuo and partitioned between Et_2O (200ml) and water (100ml). The aqueous layer was separated, extracted with Et_2O (200ml) and the combined organic layers washed with brine (200ml), dried ($MgSO_4$), and the solvent evaporated in vacuo to give a brown gum (28.6g).

8g of this material was triturated with boiling EtOH (100ml) and the resulting solid removed by filtration. The filtrate was cooled and the solid removed by filtration. The filtrate was concentrated in vacuo to give the title compound as a white solid (3g). δH ($CDCl_3$) 7.38-7.23 (3H, m, ArH), 7.14 (2H, d, J 8.7Hz, Ar-H), 6.94 (2H, d, J 8.7Hz, Ar-H), 5.24 (2H, s, CH_2OAr), 3.71 (6H, s, CO_2Me), 3.65 (1H, t, J 7.8Hz, C<u>H</u>CH_2) and 3.19 (2H, d, J 7.8Hz CHC<u>H</u>$_2$).

INTERMEDIATE 4

2-{4-[(2,6-Dichlorobenzyl)oxy]benzyl}-3-methoxy-3-oxopropanoic acid

A solution of Intermediate 3 (3.26g, 8.2mmol) in THF (35ml) and water (10ml) was treated with LiOH. H_2O (0.34g, 8.2mmol) and stirred at room temperature for 4h. The reaction was acidified to pH1 with 10% hydrochloric acid and partitioned between water (10ml) and DCM (50ml). The aqueous layer was extracted with DCM (2 x 50ml) and the combined organic layers dried ($MgSO_4$) and the solvent evaporated in vacuo to give a brown oil that was purified by chromatography (SiO_2, DCM/MeOH 9:1), to give the title compound as a gummy solid, (1.95g, 62%). δH ($CDCl_3$) 7.36-7.22 (3H, m, Ar-H), 7.15 (2H, d, J 8.6Hz, Ar-H), 6.93 (2H, d, J 8.6Hz, Ar-H), 5.22 (2H, s, CH_2OAr), 3.67 (3H, s, CO_2Me), 3.66 (1H, m, C<u>H</u>CH_2) and 3.20 (2H, d, J 7.6Hz CHC<u>H</u>$_2$).

INTERMEDIATE 5

Methyl 3-chloro-2-{4-[(2,6-dichlorobenzyl)oxy]benzyl}-3-oxopropanoate

Thionyl chloride (3.0g, 25.5mmol) was added to a solution of Intermediate 4 (1.95g, 5.1mmol) in DCM (20ml) containing 1 drop of DMF. The reaction was stirred at room temperature for 16h then concentrated *in vacuo* to give the title compound as a gum, (2.0g), which was used without further purification.

INTERMEDIATE 6

Diethyl-2-(4-nitrobenzyl)malonate

Diethyl malonate (7.41g, 46.3mmol) was added to a slurry of NaH (60% oil dispersion, 2.04g, 50.9mmol) in THF (200ml) and stirred for 15 min, before adding a solution of 4-nitrobenzyl bromide (10.0g, 46.3mmol) in THF (100ml) by cannula. The reaction was stirred for 3h at room temperature then quenched by the addition of water (100ml). The aqueous layer was separated and extracted with Et_2O (200ml). The combined organic layers were washed with brine (200ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give an off-white solid. Trituration with Et_2O/hexane (1:5, 100ml), removal of the solid by filtration and concentration of the filtrate *in vacuo* gave an oil which was purified by chromatography (SiO_2;EtOAc/hexane 1:3) to give the title compound as an oil (9.4g), containing about 20% diethyl malonate. δH ($CDCl_3$) 8.15 (2H, d, J 8.8Hz, Ar-H), 7.39 (2H, d, J 8.7Hz, Ar-H), 4.25-4.11 (4H, m, CH_2CH_3), 3.67 (1H, t, J 7.8Hz, $CHCH_2Ar$), 3.32 (2H, d, J 7.8Hz, $CHCH_2Ar$) and 1.23 (6H, t, J 7.2Hz, CH_2CH_3).

INTERMEDIATE 7

Diethyl-2-(4-aminobenzyl)malonate

Tin (II) chloride (28.8g, 0.128mmol) was added to a solution of Intermediate 6 (7.54g, 25.6mmol) in EtOH (150ml) and the reaction stirred for 72h at room temperature. The solvent was removed *in vacuo* and the residue was treated with 35% aqueous KOH (100ml), stirred for 30min and partitioned between EtOAc (200ml) and water (100ml). The organic layer was washed with brine, dried ($MgSO_4$) and the solvent evaporated *in*

vacuo to give an oil. Trituration with Et_2O/hexane (1:1, 50ml) gave the title compound (2.86g, 42%) as an off white solid. δH ($CDCl_3$) 6.99 (2H, d, J 8.4Hz, Ar-H), 6.60 (2H, d, J 8.4Hz, Ar-H), 4.15 (4H, m, CH_2CH_3), 3.57 (1H, t, J 7.8Hz, $CHCH_2Ar$), 3.57 (2H, br s, NH_2), 3.10 (2H, d, J 7.8Hz, $CHCH_2Ar$) and 1.21 (3H, t, J 7.2Hz, CH_2CH_3).

INTERMEDIATE 8

Diethyl-2-{4-[(2,6-dichlorobenzoyl)amino]benzyl}-3-oxopropanoate

A solution of 2,6-dichlorobenzoyl chloride (2.31g, 11mmol) in THF (10ml) was added to a solution of Intermediate 7 (2.86g, 10.8mmol) and NMM (1.21g, 12mmol) in THF (20ml). The reaction was stirred for 16h at room temperature then partitioned between EtOAc (50ml) and 5% hydrochloric acid (50ml). The aqueous layer was extracted with EtOAc (50ml) and the combined organic layers washed with $NaHCO_3$ solution (50ml) and brine (50ml), dried ($MgSO_4$) and the solvent removed in vacuo to give an off-white solid that was triturated with isopropyl ether to give the title compound as a white solid, (4.08g, 86%). δH ($CDCl_3$) 7.54 (2H, d, J 8.5Hz, Ar-H), 7.38-7.22 (6H, m, Ar-H, NH), 4.23-4.12 (4H, m, CH_2CH_3), 3.63 (1H, t, J 7.8Hz, $CHCH_2Ar$), 3.21 (2H, d, J 7.8Hz, $CHCH_2Ar$) and 1.23 (6H, t, J 7.1Hz, CH_2CH_3).

INTERMEDIATE 9

2-{4-[(2,6-Dichlorobenzoyl)amino]benzyl}-3-ethoxy-3-oxopropanoic acid

Aqueous KOH (1M, 9.3ml, 9.3mmol) was added to a solution of Intermediate 8 (4.05g, 9.3mmol) in dioxane (20ml) and stirred for 3h. The mixture was acidified to pH1 with 10% hydrochloric acid and extracted with DCM (3 x 25ml). The combined organic layers were dried $(MgSO)_4$ and the solvent evaporated in vacuo to give a gum that was purified by chromatography (Si_2O DCM/MeOH/AcOH 9:1:0.05) to give the title compound as a foam, (3.71g, 97%). δH ($CDCl_3$) 7.71 (1H, br s, NH), 7.58 (2H, d, J 8.5Hz, Ar-H), 7.48-7.20 (5H, m, Ar-H), 4.25-4.14 (2H, m, CH_2CH_3), 3.66 (1H, t, J 7.7Hz, $CHCH_2Ar$), 3.24 (2H, d, J 7.7Hz, $CHCH_2Ar$) and 1.26 (3H, t, J 7.2Hz, CH_2CH_3).

INTERMEDIATE 10

Ethyl-3-chloro-2-{4-[(2,6-dichlorobenzoyl)amino]benzyl}-3-oxopropanoate

Thionyl chloride (2.10g, 17.7mmol) was added to a solution of Intermediate 9 (1.45g, 3,5mmol) in DCM (20ml) and the reaction stirred at room temperature for 16h. Volatiles were evaporated in vacuo to give the title compound (1.4g) as a gummy foam which was used without further purification.

INTERMEDIATE 11

Diethyl 2-{4-[(3,5-dichloroisonicotinoyl)amino]benzoyl}malonate

A mixture of Intermediate 7 (3.6g, 13.6mmol) and triethylamine (2.1ml, 1.1equiv) in anhydrous DCM (80ml) was cooled to 5º . To this solution was added dropwise a solution of 3,5-dichloropyridyl-4-carbonyl chloride (3.3g, 1.1equiv) in 20ml of DCM. Following addition the solution was stirred at room temperature overnight. The solution was washed with water (3 x 30ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to yield the title compound (6g). δH ($CDCl_3$) 8.5 (2H, s), 7.5 (2H, d, J 8.5Hz), 7.2 (2H, d, J 8.5Hz), 4.1 (4H, m), 3.6 (1H, t, J 7.8Hz), 3.2 (2H, d, J 7.8Hz) and 1.2 (6H, m).

INTERMEDIATE 12

2-{4-[(3,5-Dichloroisonicotinoyl)amino]benzyl}-3-ethoxy-3-oxopropanoic acid

A mixture of Intermediate 11 (5g, 11.4mmol) and potassium hydroxide (0.63g, 1 equiv) in 25ml dioxane/11.5ml water was stirred for 24h at room temperature. The mixture was diluted with water (50ml), washed with DCM (10ml), acidified with 1N hydrochloric acid solution and the desired product extracted (EtOAc 2 x 75ml). The extracts were washed (brine, 30ml), dried ($MgSO_4$), and the solvent evaporated in vacuo, to yield the title compound (3.2g) as a white solid. δH ($CDCl_3$) 8.4 (2H, s), 7.4 (2H, d, J 8.5Hz), 7.2 (2H, d, J 8.5Hz), 4.0 (2H, q, J 7.8Hz), 3.5 (1H, t, J 7.8Hz), 3.0 (2H, d, J 7.8Hz) and 1.1 (3H, t, J 7.1Hz).

INTERMEDIATE 13

Ethyl-3-chloro-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoate

Intermediate 12 (1.5g, 3.8mmol) was stirred for 24h in anhydrous DCM (20ml) and thionyl chloride (1.3mg, 5 equiv). The solvent and excess thionyl chloride were evaporated in vacuo, azeotroping once with toluene, to yield the title compound (1.6g) as a gummy solid. δH ($CDCl_3$) 8.9 (2H, s), 7.7 (2H, d, J 8.5Hz), 7.2 (2H, d, J 8.5Hz), 4.2 (2H, m), 4.1 (1H, t, J 7.9Hz), 3.3 (2H, d, J 7.9Hz) and 1.3 (3H, t, J 7.0Hz).

EXAMPLE 1

Methyl 2-{4-[(2,6-dichlorobenzyl)oxy]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoate

A solution of 2,6-dimethoxyaniline (0.40g, 2.6mmol) in THF (5ml) was added to a slurry of NaH (60% dispersion in oil, 126mg, 3.1mmol) in THF (5ml), the mixture stirred for 30mins and a solution of Intermediate 5 (1.05g, 2.6mmol) in THF (10ml) added. The reaction was stirred for 3h then quenched with water, partitioned between DCM (50ml) and 10% hydrochloric acid (20ml). The aqueous layer was extracted with DCM (20ml) and the combined organic layers washed with $NaHCO_3$ solution (50ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellowish foam which was purified by chromatography (SiO_2, gradient elution, hexane/EtOAc 3:1 to 1:1) to give the title compound as a white solid, (0.98g, 73%). δH ($CDCl_3$) 7.37 (1H, br s, NH), 7.35-7.14 (6H, m, Ar-H), 6.94 (2H, m, Ar-H), 6.56 (2H, d, J 8.6Hz, Ar-H), 5.24 (2H, s, CH_2OAr), 3.78 (6H, s, OMe), 3.71 (3H, s, CO_2Me), 3.66 (1H, m, C<u>H</u>CH_2) and 3.30 (2H, m, CHC<u>H_2</u>).

EXAMPLE 2

2-{4-[(2,6-Dichlorobenzyl)oxy]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid

$LiOH.H_2O$ (120mg, 2.9mmol) was added to a solution of the compound of Example 1 (0.98g, 1.9mmol) in THF (10ml) and water (5ml) and the reaction stirred at room temperature for 1.5h, then acidified to pH1 with 10% hydrochloric acid and extracted with DCM (2 x 25ml). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated in vacuo to

give a white foam that was triturated with DCM/Et_2O to give the title compound as a white solid (0.52g, 54%). δH (DMSO d_6) 9.09 (1H, br s, NH), 7.58-7.44 (3H, m, Ar-H), 6.98 (2H, d, J 8.4Hz, Ar-H), 6.65 (2H, d, J 8.4Hz, Ar-H), 5.20 (2H, s, CH_2OAr), 3.69 (6H, s, OMe), 3.69 (1H, m, $CHCH_2$) and 3.05 (2H, m, $CHCH_2$). m/z (ESI, 60V) 504, 506 (MH^+).

EXAMPLE 3

Methyl 2-{4-[(2,6-dichlorobenzyl)oxy]benzyl}-3-[2-chloro-5-(2-ethoxy-2-oxoethyl)anilino]-3-oxopropanoate

A solution of 2-chloro-5-(2-ethoxy-2-oxoethyl)aniline (0.40g, 1.42mmol) in THF (5ml) was added to a solution of Intermediate 5 (1.04g, 2.6mmol) and NMM (0.30g, 3.0mmol) in THF (10ml) and stirred for 16h at room temperature. The reaction was partitioned between EtOAc (25ml) and 10% hydrochloric acid (20ml) and the organic layer washed with $NaHCO_3$ solution (2 x 20ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow gum that was triturated with Et_2O to give the title compound as an off white solid (0.45g, 58%). δH ($CDCl_3$) 8.88 (1H, br s, NH), 8.30 (1H, d, J 1.9Hz, Ar-H), 7.37-7.21 (6H, m, Ar-H), 7.15 (2H, d, J 8.6Hz, Ar-H), 6.99 (1H, dd, J 2.1, 8.2Hz, Ar-H), 6.95 (2H, d, J 8.6Hz), 5.24 (2H, s, CH_2OAr), 4.15 (2H, q, J 7.1Hz, CH_3CH_3), 3.73 (3H, s, CO_2Me), 3.67 (1H, dd, J 6.6, 8.2Hz, CH_2CH_3)), 3.73 (3H, s, CO_2Me), 3.67 (1H, dd, J 6.6, 8.2Hz, $CHCH_2$), 3.60 (2H, s, CH_2CO_2Et), 3.30 (2H, m, $CHCH_2$) and 1.26 (3H, t, CH_2CH_3).

EXAMPLE 4

3-[5-(Carboxymethyl)-2-chloroanilino]-2-{4-[(2,6-dichlorobenzyl)oxy]benzyl}-3-oxopropanoic acid.

LiOH .H_2O (72mg, 1.72mmol) was added to a solution of the compound of Example 3 (0.45g, 0.82mmol) in THF (10ml) and water (5ml). The reaction was stirred for 1h at room temperature, then acidified to pH1 with 10% hydrochloric acid and extracted with DCM (2 x 25ml). The combined organic layers were dried ($MgSO_4$) and solvent evaporated in vacuo to give a gum which was triturated with Et_2O/DCM (1:1) to give the title compound as a white solid (180mg, 41%). δH (DMSO d_6) 9.69 (1H, s, NH), 7.57-7.38 (5H, m, ArH), 7.21 (2H, d, J 8.6Hz, ArH), 7.07 (1H, dd, J 2.1, 8.3Hz, ArH), 6.97 (2H, d, J 8.6Hz, Ar-H), 5.18 (2H, s, CH_2OAr), 3.93

(1H, m, C<u>H</u>CH_2), 3.56 (2H, s, C<u>H_2</u>CO_2H) and 3.07 (2H, m, CHC<u>H_2</u>). M/Z (ESI, 60V) 536, 538 (MH^+).

EXAMPLE 5

Ethyl-2-{4-[(2,6-dichlorobenzoyl)amino]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoate

A solution of Intermediate 10 (0.70g, 1.68mmol) in THF (10ml) was added to a solution of 2,6-dimethoxyaniline (0.20g, 1.31mmol) and NMM (0.20g, 2.0mmol) in THF (10ml). The reaction was stirred at room temperature for 16h then partitioned between water (20ml) and EtOAc (20ml), the organic layer separated and washed with 10% hydrochloric acid (10ml), $NaHCO_3$ solution (10ml) and brine (10ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give a solid which was triturated with boiling EtOAc (10ml) to give the title compound, (0.59g, 64%) as a white solid. δH (DMSO d_6) 9.10 (1H, s, NH), 7.62-7.47 (5H, m, Ar-H), 7.26 (2H, d, J 8.4, Ar-H), 4.10 (2H, m, C<u>H_2</u>CH_3), 3.82 (1H, t, J 7.4Hz, C<u>H</u>CH_2), 3.69 (6H, s, OMe), 3.07 (2H, d, J 7.4Hz, CHC<u>H_2</u>) and 1.19 (3H, t, J 7.1Hz, CH_2C<u>H_3</u>).

EXAMPLE 6

2-{4-[(2,6-Dichlorobenzoyl)amino]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid

A solution of the compound of Example 5 (0.59g, 1.1mmol) in EtOH (5ml), THF (2ml) and water (2ml) was treated with KOH (1M aqueous solution, 1.62ml, 1.62mmol) and the reaction stirred for 2.5h. The mixture was concentrated *in vacuo* and acidified to pH1 with 10% hydrochloric acid, to give a white precipitate which was isolated by filtration and washed with water, triturated with boiling MeOH and washed with Et_2O to give the title compound as a white solid (300mg, 54%). δH (DMSO d_6) 10.65 (1H, s, NH), 9.04 (1H, s, NH), 7.6-7.46 (5H, m, Ar-H), 7.28-7.16 (3H, m, Ar-H), 6.65 (2H, d, J 8.4Hz, Ar-H), 3.74 (1H, m, C<u>H</u>CH_2), 3.68 (6H, s, OMe), 3.30 (1H, m, CHC<u>H_A</u>H_B) and 3.06 (1H, m, CHCH_A<u>H_B</u>). m/z (ESI, 60V) 517, 519 (MH^+).

EXAMPLE 7

Ethyl 3-(2,6-dichloroanilino)-2-{3-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoate

Intermediate 13 (350mg, 0.8mmol) in anhydrous DCM (2ml) was added dropwise to a mixture of 2,6-dichloroaniline (133mg, 1 equiv) and triethylamine (0.12ml, 1.1equiv), dissolved in DCM (10ml) at 5°. The mixture was stirred for 16h at room temperature, then quenched with water (2ml) The solvent was removed, and the residue dissolved in EtOAc. The resulting solution was washed with water, (2 x 10ml), brine (10ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was slurried in Et_2O and the title compound (360mg) isolated by filtration. δH ($CDCl_3$) 8.5 (2H, s), 7.5 (2H, d, J 8.5Hz), 7.25 (2H, d, J 8.5Hz), 7.2 (2H, d, J 8.5Hz), 7.1 (1H, t, J 8.5Hz), 4.1 (2H, q, J 7.0Hz), 3.7 (1H, t, J 7.9Hz), 3.2 (2H, d, J 7.9Hz) and 1.1 (3H, t, J 7.0Hz). m/z/ (ESI, 60V) 554 $(M + H)^+$.

EXAMPLE 8

Ethyl-3-(2,6-dimethoxyanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoate

The title compound was prepared using the method of Example 6, substituting 2,6-dimethoxyaniline for 2,6-dichloroaniline. The title compound was isolated as white solid, (64%). δH ($CDCl_3$ + few drops CD_3OD) 8.5 (2H, s), 7.5 (2H, broad signal), 7.2 (2H, broad signal), 7.1 (1H, broad triplet), 6.5 (2H, d, J 8.4Hz), 4.1 (2H, broad signal), 3.7 (6H, s), 3.6 (1H, broad signal), 3.3 (2H, broad signal), 3.0 (3H, s) and 1.2 (3H, t, J 7.2H.z). m/z (ESI, 60V) 546 $(M + H)^+$.

EXAMPLE 9

Ethyl 2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-(3,5-dichloro-4-pyridinyl)-3-oxopropanoate

3,5 Dichloro-4-aminopyridine (190mg, 1.2mmol) dissolved in anhydrous THF (5ml) was added dropwise to a suspension of sodium hydride (68%, 150mg, 3.2equiv) in anhydrous THF (2ml) at 5°. Following addition the mixture was stirred at room temperature for 10 min, recooled to 5° and Intermediate 13 (0.5g, 1 equiv) in anhydrous THF (5ml) was added in one portion. The mixture was stirred at room temperature for 16h, quenched with water, and diluted with EtOAc (50ml). The organic layer was isolated and washed with water (2 x 10ml), brine (10ml) dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was slurried in Et_2O and the title

compound (300mg) was isolated by filtration. δH (CD_3OD + few drops DMSO d_6) 8.7 (2H, s), 8.6 (2H, s), 7.6 (2H, d, J 8.9Hz), 7.4 (2H, d, J 8.9Hz), 4.3 (2H, d, J 8.9Hz), 7.4 (2H, d, J 8.9Hz), 4.3 (2H, q, J 7.2Hz), 4.1 (1H, m), 3.3 (2H, m) and 1.3 (34H, t, J 7.2Hz). m/z (ESI, 60V) 554 $(M + H)^+$.

EXAMPLE 10

3-(2,6-Dichloroanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoic acid

The compound of Example 7 (350mg, 0.6mmol) and LiOH. H_2O (40mg, 1.5 equiv) were stirred for 16h in a mixture of MeOH (10ml), water (5ml) and THF (5ml). The solvents were removed *in vacuo* and the residue dissolved in water (5ml). The solution was acidified and extracted with EtOAc (3 x 20ml). The combined extracts were washed with water (2 x 10ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound (290mg) as a white solid. δH (DMSO) 10.8 (1H, s), 10.1 (1H, s), 8.8 (2H, s), 7.6 (2H, d, J 8.5Hz), 7.5 (2H, d, J 8.0Hz), 7.3 (3H, m), 3.8 (1H, t) and 3.1 (2H, m). m/z (ESI, 60V) 526 $(MH)^+$.

The compounds of Examples 11 and 12 were prepared in a similar manner to the compound of Example 10:

EXAMPLE 11

3-(2,6-Dimethoxyanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoic acid

From the compound of Example 8. The title compound was isolated as a white solid (69%). δH (DMSO d_6) 10.8 (1H, s), 8.7 (2H, s), 7.5 (2H, d, J 8.4Hz), 7.3 (2H, d, J 8.4Hz), 7.2 (1H, t, J 8.4Hz), 6.6 (2H, d, J 8.4Hz), 3.7 (7H, s) and 3.0 (2H, d, J 7.5Hz). m/z (ESI) 518 $(M+H)^+$.

EXAMPLE 12

2-{4-[(3,5-Dichloroisonicotinoyl)amino]benzyl}-3-[(3,5-dichloro-4-pyridinyl)amin]-3-oxopropanoic acid

From the compound of Example 9. The title compound was isolated as a white solid (20%). δH (DMSO d_6) 10.8 (1H, s), 10.4 (1H, s), 8.8 (2H, s),

8.6 (2H, s), 7.6 (2H, d, J 8.5Hz), 7.3 (2H, d, J 8.5Hz), 3.9 (1H, t) and 3.2 (2H, m). m/z (ESI) 526 $(M+H)^+$.

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5 x 10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5μg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100μl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200μl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200μl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100μl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50μg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

αIIb/β_3 -dependent human platelet aggregation

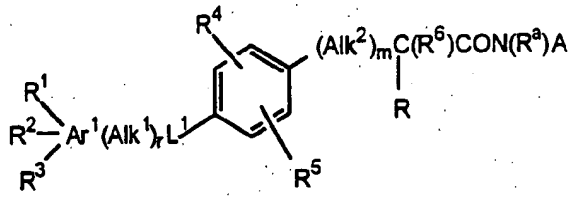
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0;

$NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the preferred compounds of the invention generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1):



(1)

wherein

Ar^1 is an aromatic or heteroaromatic group;

R^1, R^2, R^3, R^4 and R^5 which may be the same or different is each an atom or group $-L^2(Alk^3)_tL^3(R^7)_u$ in which L^2 and L^3 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^3 is an aliphatic or heteroaliphatic chain and R^7 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-SR^8$, $-NR^8R^9$ [where R^9 is as just defined for R^8 and may be the same or different], $-NO_2$, -CN, $-CO_2R^8$, $-SO_3H$, $-S(O)R^8$, $-SO_2R^8$, $-OCO_2R^8$, $-CONR^8R^9$, $-OCONR^8R^9$, $-CSNR^8R^9$, $-COR^8$, $-OCOR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^9)(R^{10})$, [where R^{10} is a hydrogen atom or an optionally substituted alkyl group] $-N(R^8)CSN(R^9)(R^{10})$ or $-N(R^8)SO_2N(R^9)(R^{10})$;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a covalent bond or a linker atom or group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^6 is a hydrogen atom or a methyl group;

r is zero or the integer 1;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

R^a is a hydrogen atom or a methyl group;

A is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which R is a $-CO_2H$ group.

3. A compound according to Claim 1 or 2 in which Alk^2 is a $-CH_2-$ chain and m is the integer 1.

4. A compound according to Claim 1 to Claim 3 in which R^6 and R^a is each a hydrogen atom.

5. A compound according to Claim 1 to Claim 4 in which Ar^1 is a phenyl, pyridyl or pyrimidinyl group, wherein R^1 and R^2 is each a halogen atom or alkyloxy or haloalkyloxy group and R^3 is hydrogen.

6. A compound according to Claim 1 to Claim 5 in which $(Alk^1)_rL^1$ is a $-CH_2O-$ or $-CON(R^{11})-$ group.

7. A compound according to any one of the preceding claims in which A is an optionally substituted phenyl or pyridyl group.

8. A compound which is:
3-(2,6-Dichloroanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoic acid;
3-(2,6-Dimethoxyanilino)-2-{4-[(3,5-dichloroisonicotinoyl)amino]benzyl}-3-oxopropanoic acid;
2-{4-[3,5-Dichloroisonicotinoyl)amino]benzyl}-3-[(3,5-dichloro-4-pyridinyl)amino]-3-oxapropanoic acid;
2-{4-[(2,6-Dichlorobenzoyl)amino]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid;
2-{4-[(2,6-Dichlorobenzyl)oxy]benzyl}-3-(2,6-dimethoxyanilino)-3-oxopropanoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

9. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Inte: ɔnal Application No
PCT/GB 99/03243

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/81 C07C235/80 A61K31/4427 A61K31/44 A61K31/185

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ¹	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 28 37 264 A (SHIONOGI & CO) 1 March 1979 (1979-03-01) page 2, line 34 -page 3, line 10	1
A	WO 93 09795 A (YEDA RES & DEV ;FRIEDMAN MARK M (IL)) 27 May 1993 (1993-05-27) page 6, line 1 - line 34; claims 1,23-25	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

¹ Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2000	14/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03243

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 3-7, 9 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 3-7, 9 (in part)

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, the expression "....or a derivative thereof...." (cf. the definition of the substituent group R in the present claim 1) is considered to be unclear in the sense of Article 6 PCT since this term is non-limiting as regards the structure of the compounds of formula (1). Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the examples and to the compounds of the present formula (1) wherein R is a carboxylic acid (-COOH) group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter ..nal Application No
PCT/GB 99/03243

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2837264 A	01-03-1979	JP 1287855 C	14-11-1985
		JP 54036288 A	16-03-1979
		JP 60009718 B	12-03-1985
		AR 220539 A	14-11-1980
		AT 361121 B	25-02-1981
		AT 620378 A	15-07-1980
		AU 517618 B	13-08-1981
		AU 3923878 A	28-02-1980
		BE 869955 A	18-12-1978
		BG 34338 A	15-08-1983
		CA 1101417 A	19-05-1981
		CH 637396 A	29-07-1983
		CS 203927 B	31-03-1981
		DD 137230 A	22-08-1979
		DK 372878 A	26-02-1979
		ES 472817 A	16-02-1979
		FI 782586 A,B,	26-02-1979
		FR 2401165 A	23-03-1979
		GB 1576796 A	15-10-1980
		GR 70260 A	02-09-1982
		HU 177900 B	28-01-1982
		IE 47630 B	16-05-1984
		IT 1118098 B	24-02-1986
		MX 5328 E	22-06-1983
		NL 7808802 A,B,	27-02-1979
		NO 782866 A	27-02-1979
		NZ 188173 A	15-05-1981
		PH 17508 A	07-09-1984
		PT 68434 A	01-09-1978
		RO 75070 A	30-10-1980
		SE 452010 B	09-11-1987
		SE 7808950 A	26-02-1979
		US 4201782 A	06-05-1980
		YU 202878 A	31-10-1982
		ZA 7804753 A	29-08-1979
WO 9309795 A	27-05-1993	AT 158589 T	15-10-1997
		AU 3141693 A	15-06-1993
		CA 2117282 A	27-05-1993
		DE 69222433 D	30-10-1997
		EP 0617705 A	05-10-1994
		JP 7503944 T	27-04-1995
		US 5519005 A	21-05-1996
		US 5352667 A	04-10-1994